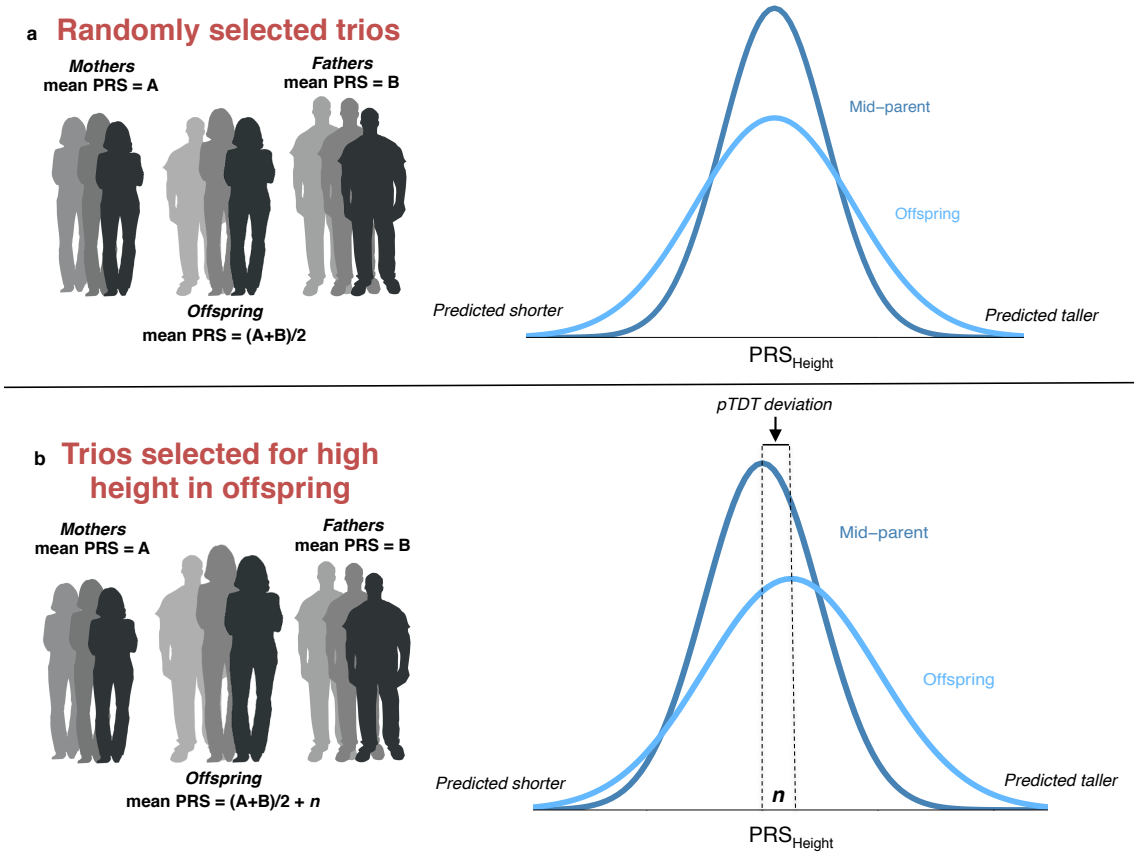
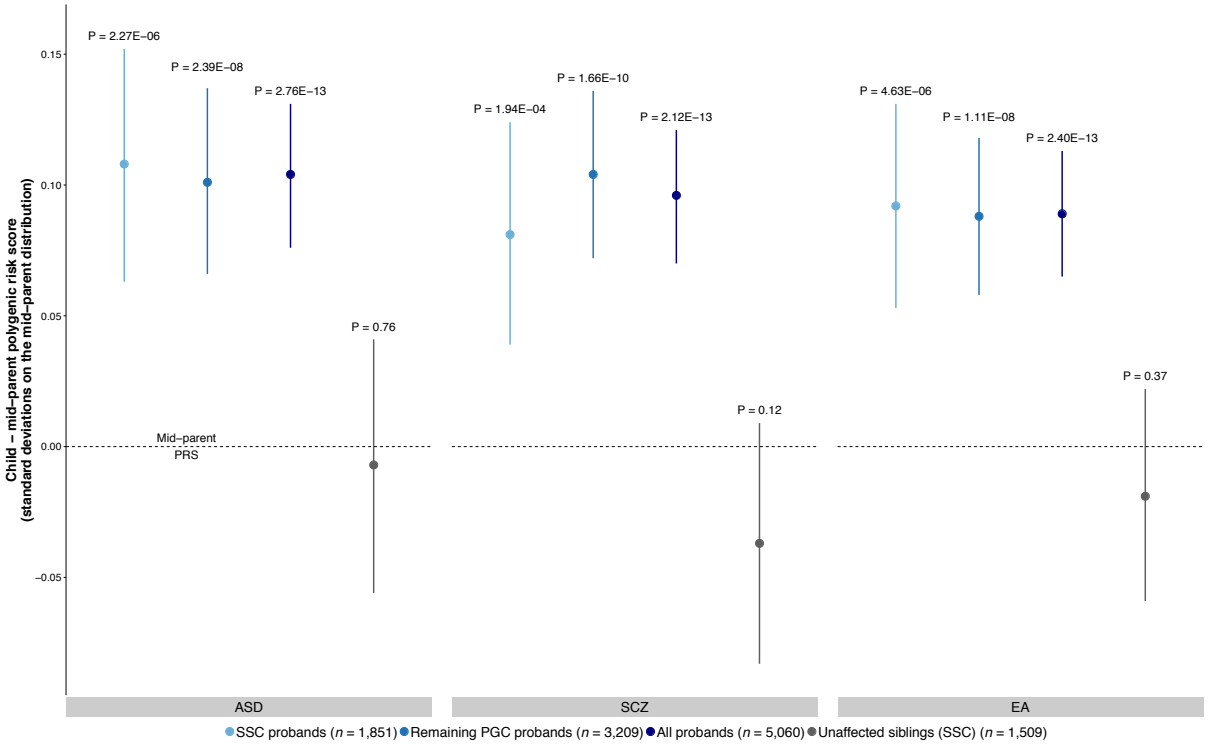


Supplementary Figure 1

Illustrative example of pTDT using height

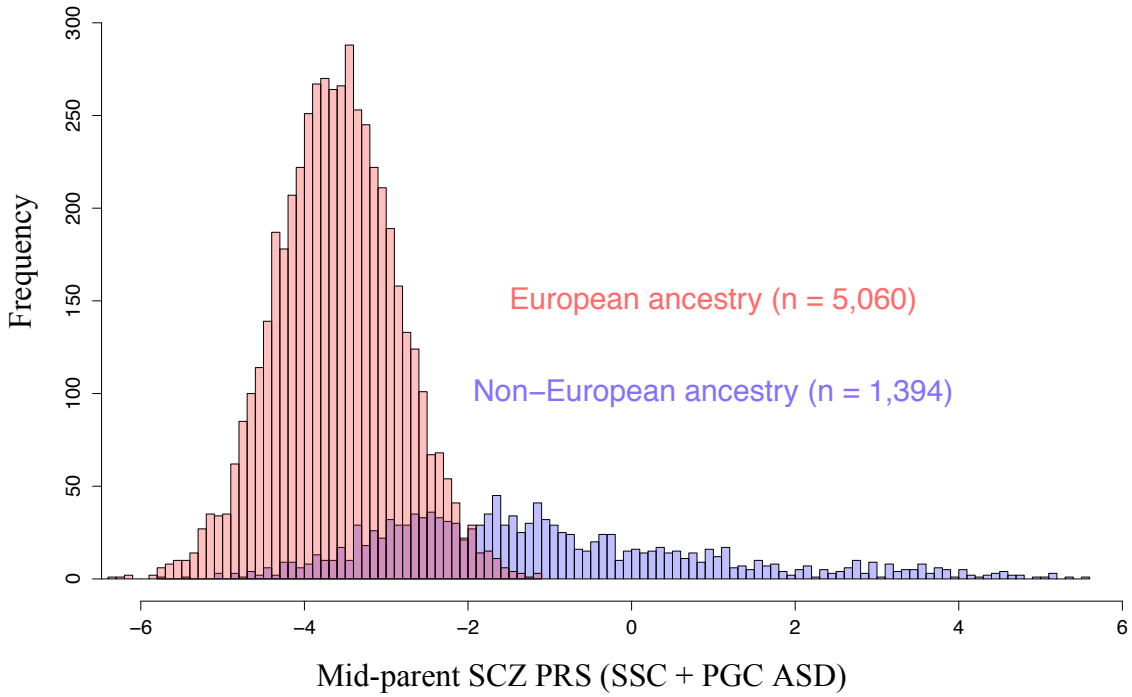
The expected value of a child's polygenic risk score (PRS) for a trait is the average of maternal and paternal PRS values. For example, if a mother's PRS is A, the expected PRS of an egg, which contains half of the maternal genetic material, is A/2. If the father's PRS is B, the expected PRS of a sperm is B/2. The expected value of the child's PRS is then (A+B)/2. (**a**) In a randomly selected cohort of parent-child trios, the average of the children's polygenic risk scores (PRS) for height, in light blue, is expected to equal the average of the mid-parent PRS for height, in dark blue; for each pair of parents, the mid-parent PRS is calculated by averaging the maternal and paternal PRS; the variance of the mid-parent PRS is reduced because it is the average of the maternal and paternal values. (**b**) In a cohort of trios phenotypically selected for very high height in the offspring (offspring who are taller than expected based on the height of the parents), we expect offspring PRS to exceed mid-parent PRS. The difference between the mean of the offspring PRS distribution and mid-parent PRS distribution, *n*, we refer to as polygenic transmission disequilibrium.



Supplementary Figure 2

ASD probands of European ancestry over inherit ASD-associated polygenic risk

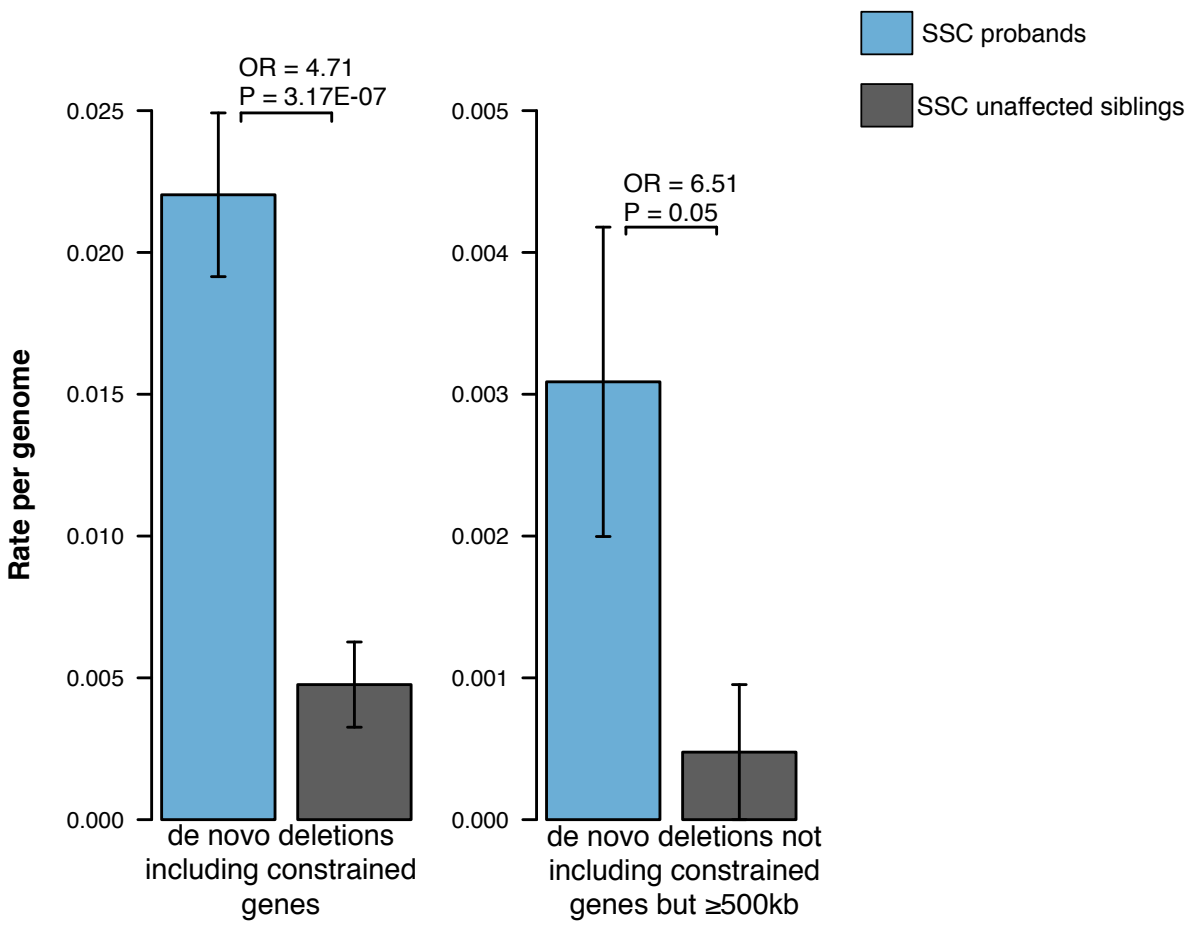
We performed pTDT after restricting the cohort to European ancestry (**Supplementary Note 4**; n = 1,851 SSC Probands, n = 3,209 PGC ASD Probands, n = 5,060 SSC and PGC ASD Probands combined, n = 1,509 SSC unaffected siblings). Transmission disequilibrium is shown in terms of standard deviations on mid-parent distribution ± 1.96 standard error (95% confidence intervals). P-values denote the probability that the mean of the pTDT deviation distribution is 0 (two-sided, one-sample t-test).



Supplementary Figure 3

Polygenic risk for schizophrenia stratifies by ancestry

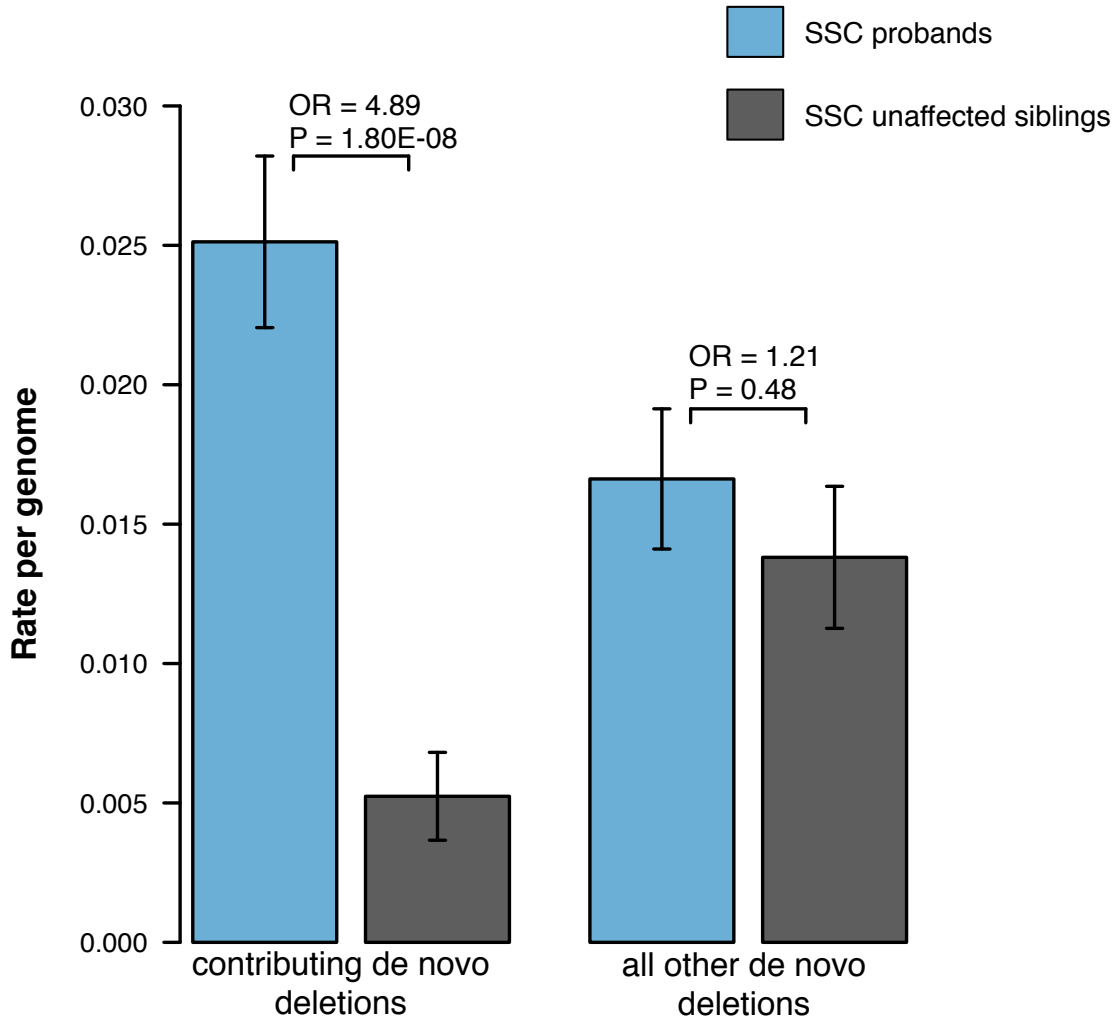
See **Supplementary Note 4** for discussion of ancestral stratification of schizophrenia polygenic risk score.



Supplementary Figure 4

Large *de novo* deletions and *de novo* deletions in constrained genes were associated with ASD case status

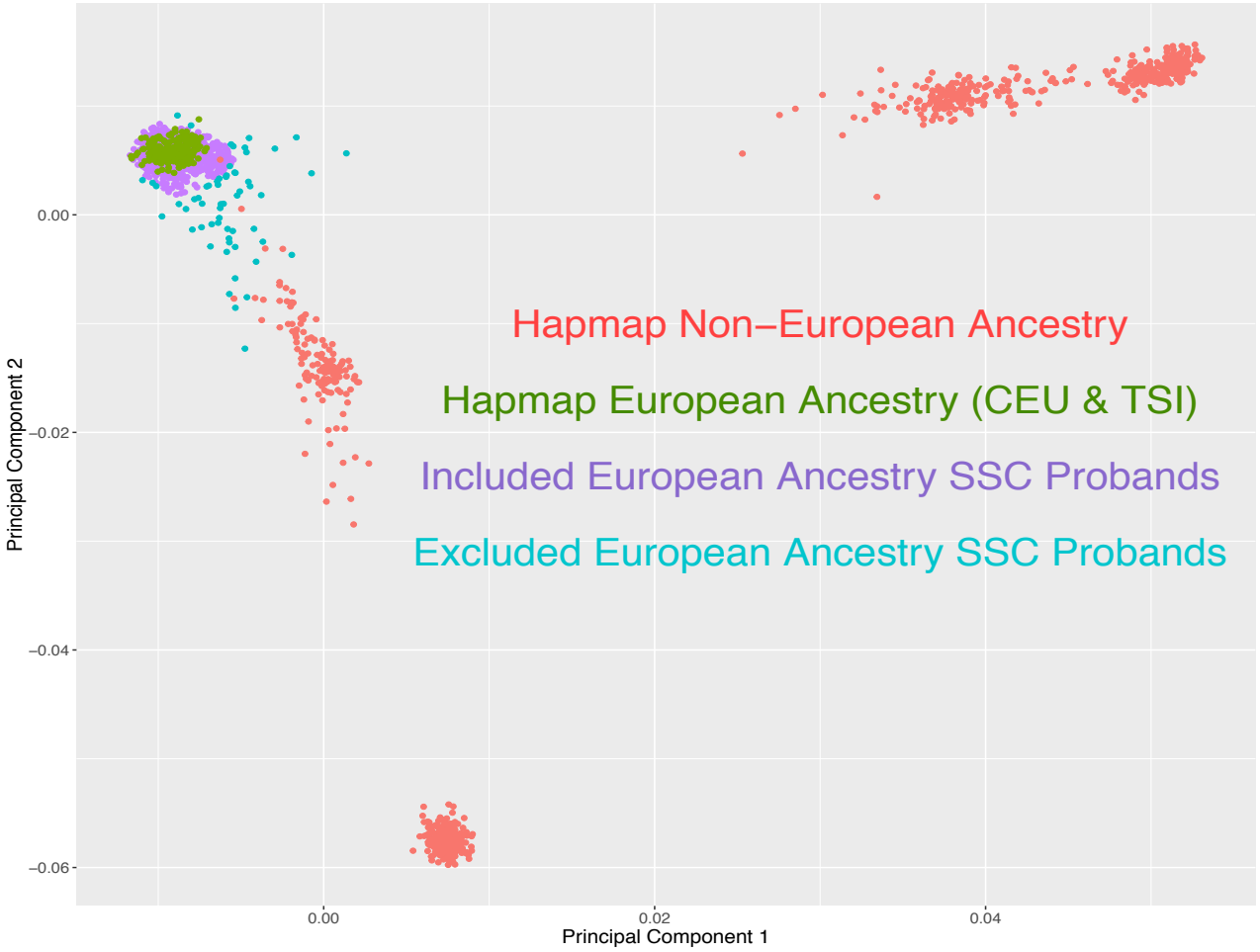
Constrained genes are intolerant of heterozygous loss of function variations (probability of being loss-of-function intolerant (pLI) ≥ 0.9); p-values are from Fisher's exact test and estimate the probability with which the variant type is equally likely to be seen in cases (n = 2,587 subjects) and controls (n = 2,100 subjects); error bars are ± 1 standard error.



Supplementary Figure 5

Unconstrained *de novo* deletions were not associated with ASD case status

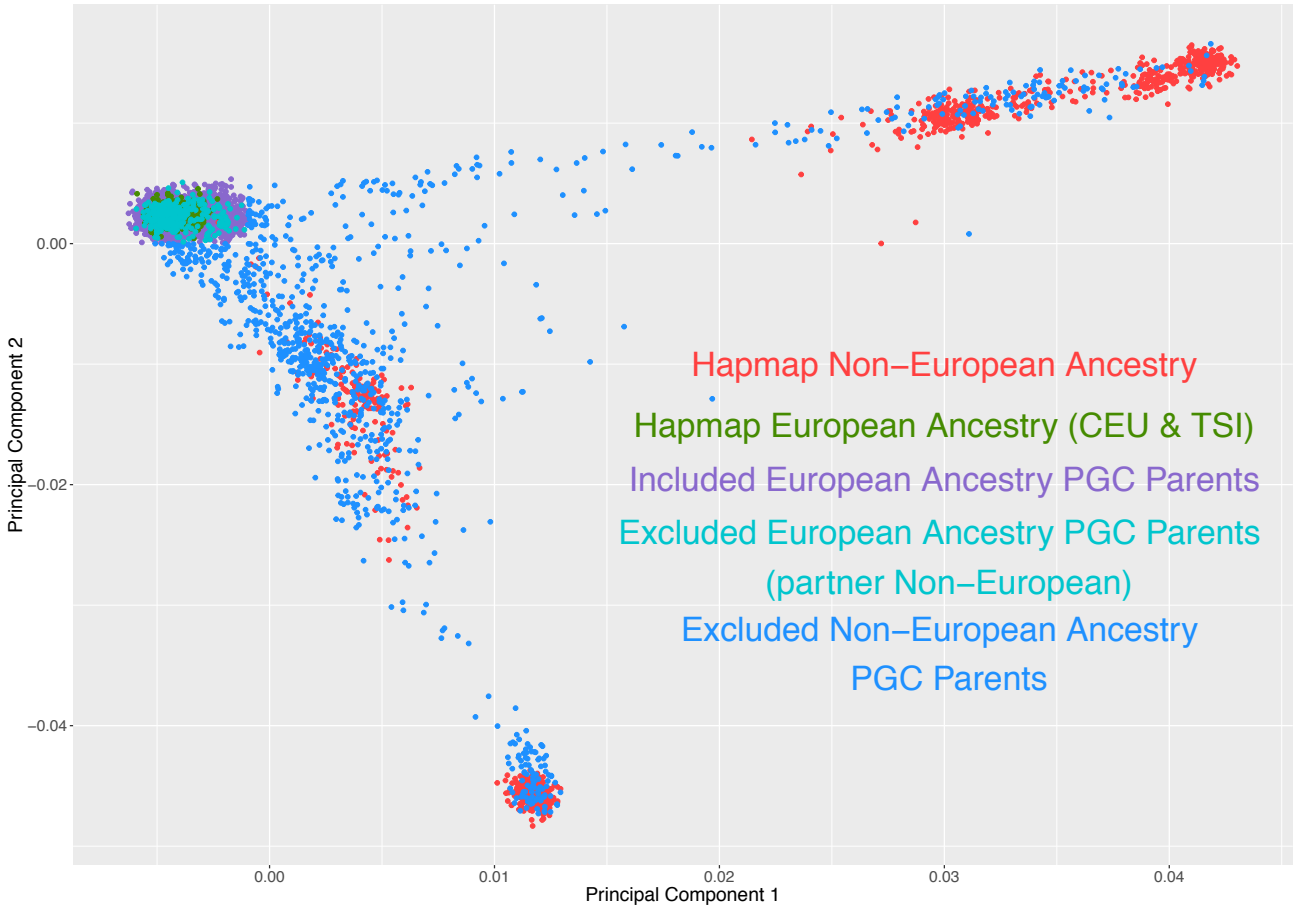
Contributing deletions are deletions in either category in **Supplementary Figure 4** (constrained or ≥ 500 kb and unconstrained); error bars are ± 1 standard error; p-values are from Fisher's exact test and estimate the probability that the variant type is equally likely to be seen in cases (n = 2,587 subjects) and controls (n = 2,100 subjects).



Supplementary Figure 6

Ancestry of Simons Simplex Collection Probands

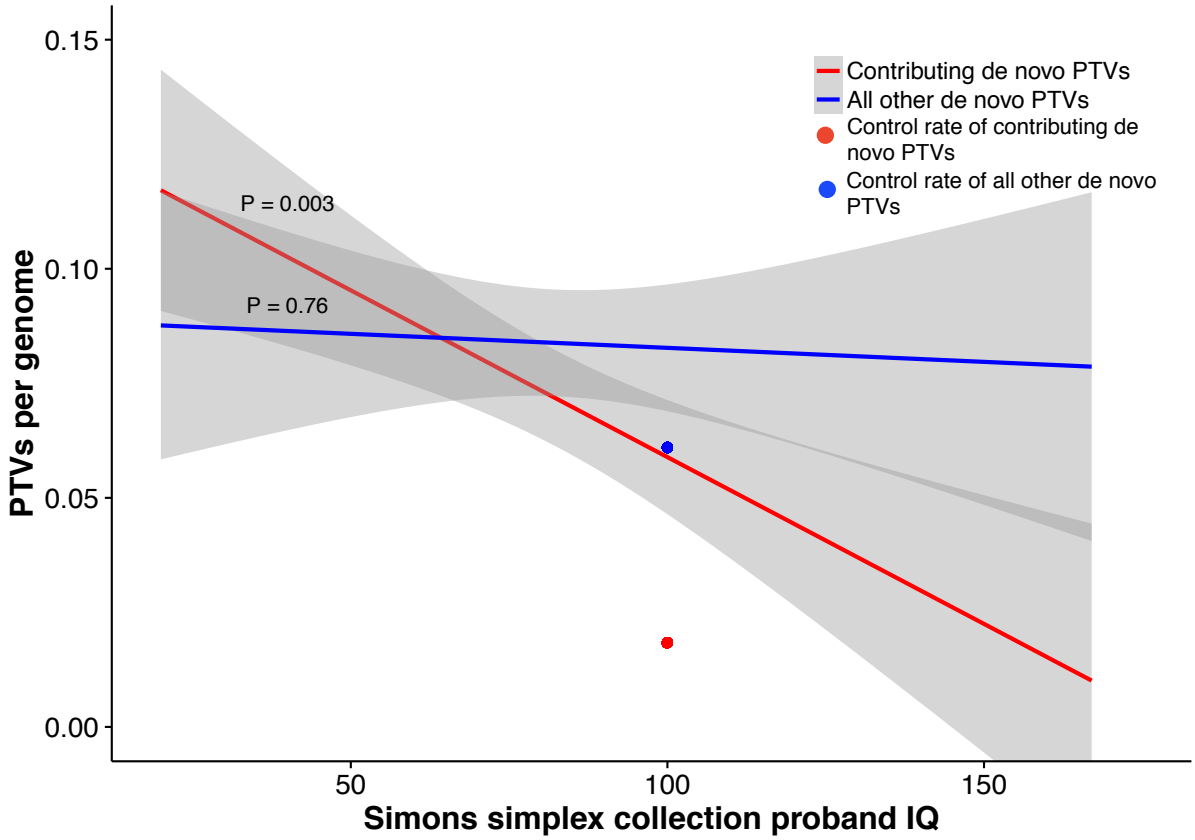
Included/excluded denotes whether first two proband principal components of ancestry are within the study-defined bounds of European ancestry; Hapmap population CEU = Individuals of Northern and Western European ancestry residing in Utah, USA; Hapmap population TSI = Tuscans in Italy; Non-European = All Hapmap cohorts excluding CEU & TSI; see **Online Methods:** ***Sample Description*** for more information.



Supplementary Figure 7

Ancestry of parents of ASD probands in Psychiatric Genomics Consortium Autism Group

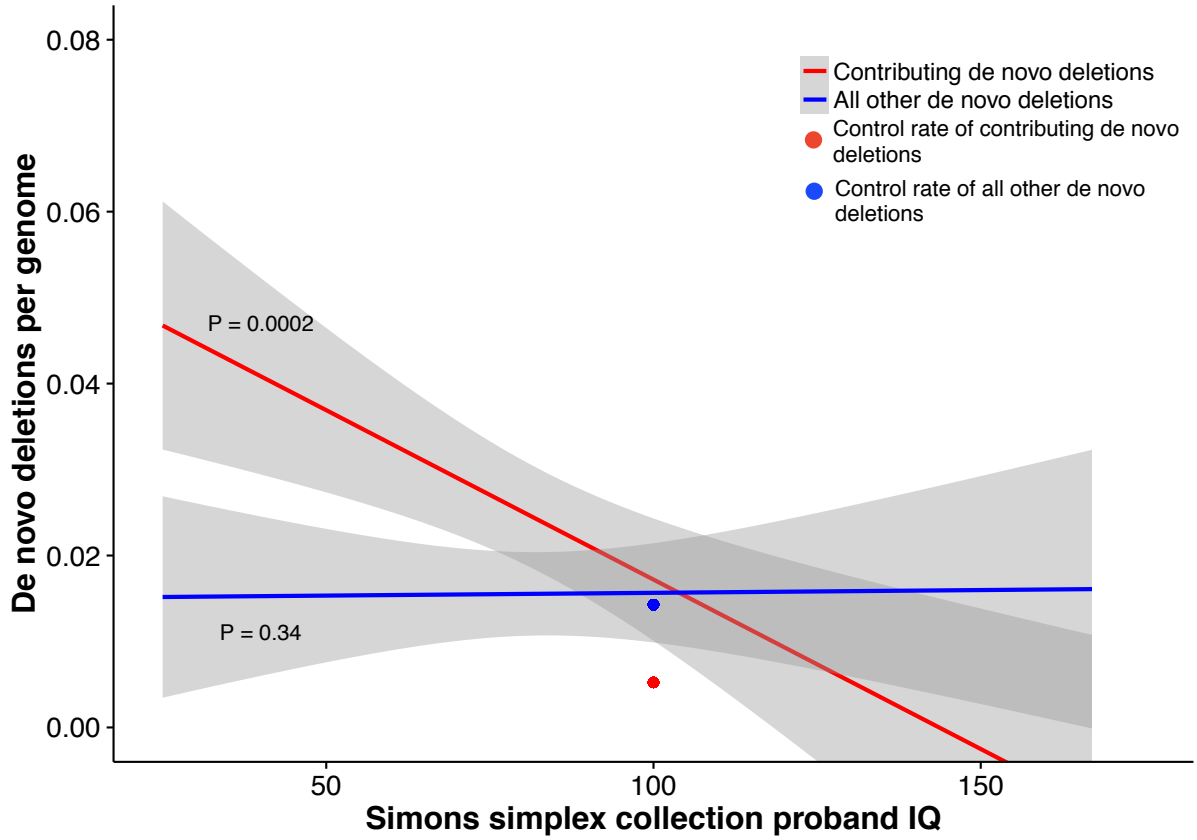
Included/excluded denotes whether first two parent principal components of ancestry are within the study-defined bounds of European ancestry; families were marked as European ancestry if both parents were marked as included; Hapmap population CEU = Individuals of Northern and Western European ancestry residing in Utah, USA; Hapmap population TSI = Tuscans in Italy; Non-European = All Hapmap cohorts excluding CEU & TSI; see **Online Methods:** ***Sample Description*** for more information.



Supplementary Figure 8

Association between constrained PTV rate and proband IQ in SSC

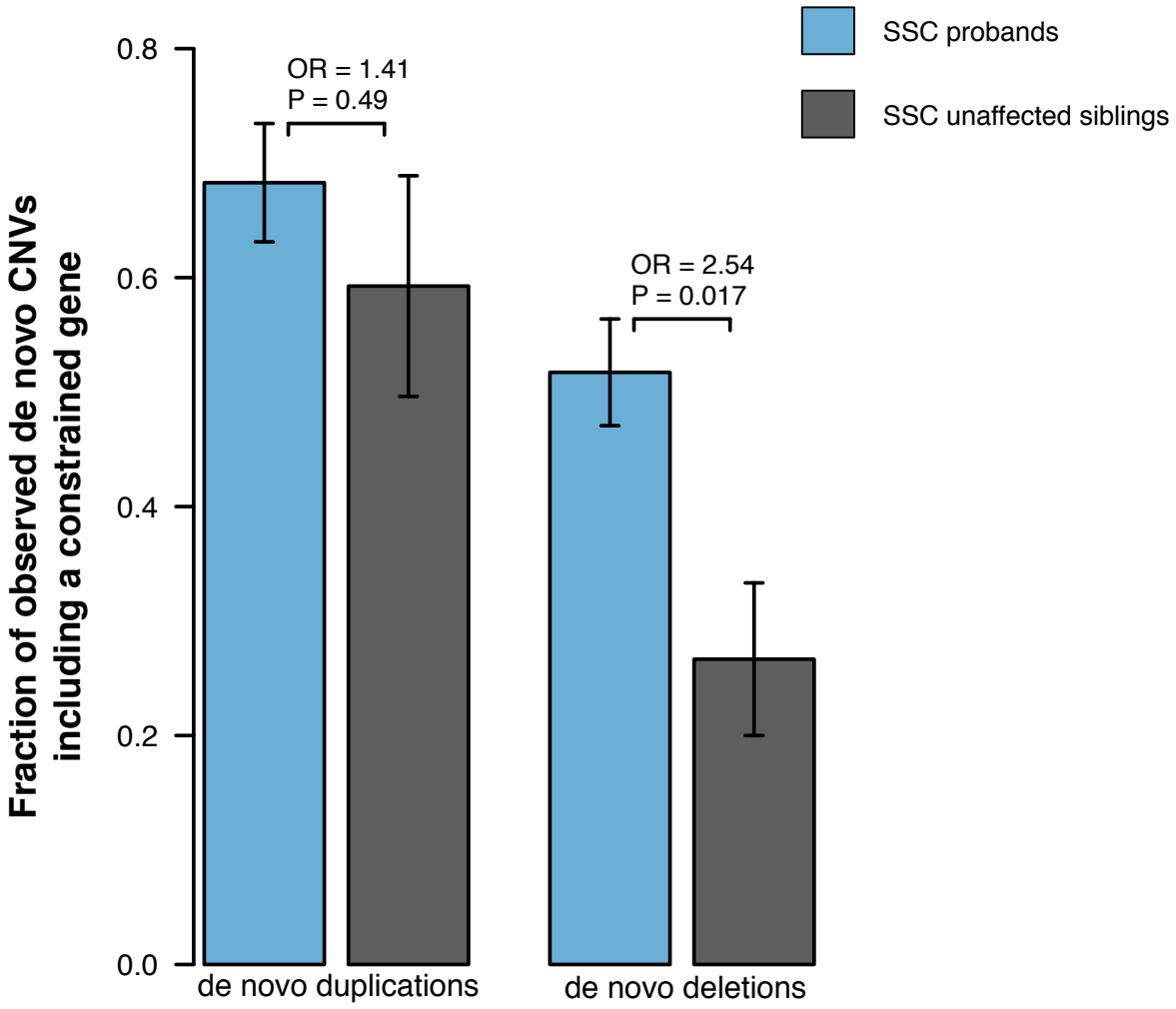
The red line denotes the linear relationship between contributing PTVs (**Online Methods: De novo *variant analyses***) and full-scale IQ in SSC probands (n = 2,492 subjects); the blue line denotes the linear relationship between all other PTVs and full-scale IQ in SSC probands (n = 2,492 subjects); shaded regions denote 95% confidence interval; red line p-value is associated with a Poisson regression predicting count of contributing *de novo* PTVs from proband IQ and proband sex, and estimates the probability of no association between proband IQ and rate of contributing *de novo* PTVs; blue line p-value is associated with a Poisson regression predicting count of non-contributing *de novo* PTVs from proband IQ and proband sex and estimates the probability of no association between proband IQ and rate of non-contributing *de novo* PTVs; control rate dots are calculated from n = 1,902 unaffected sibling controls.



Supplementary Figure 9

Association between contributing deletions and proband IQ in SSC

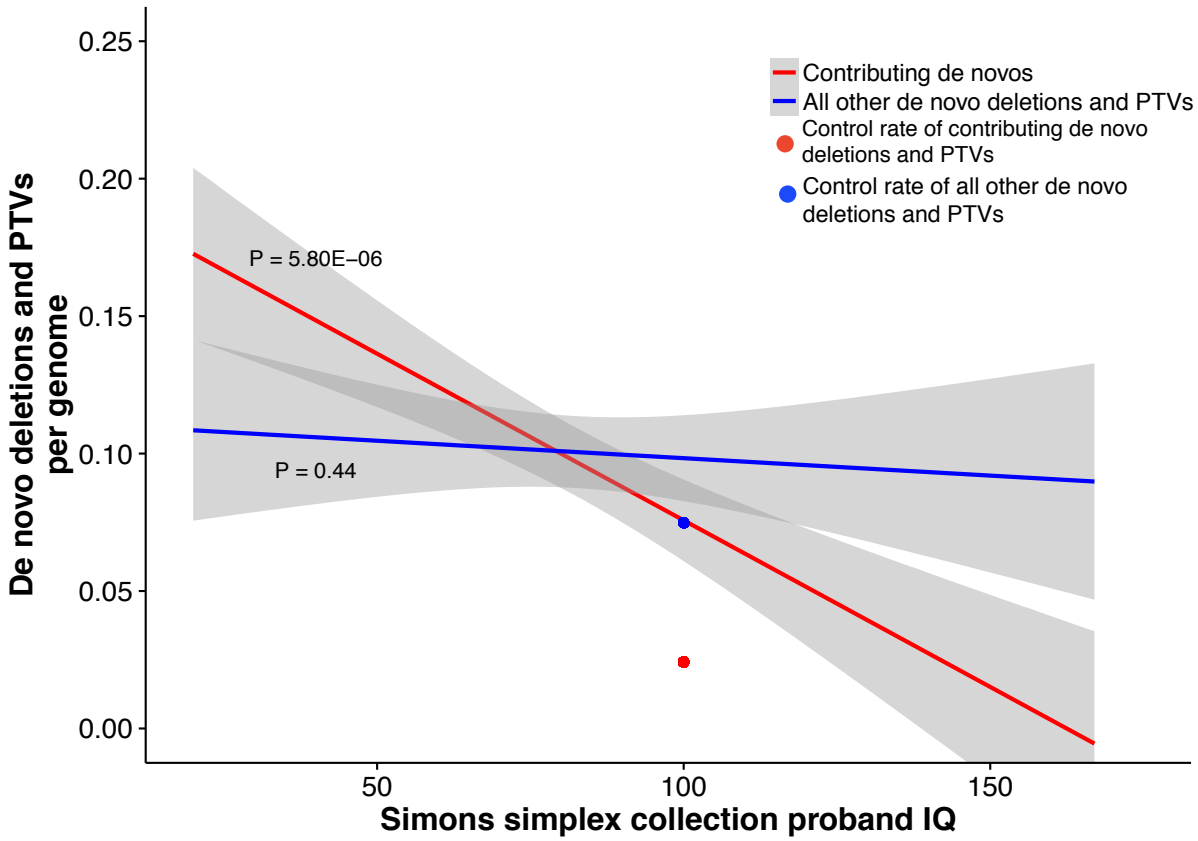
The red line denotes the linear relationship between rate of contributing deletions (**Online Methods: De novo *variant analyses***) and full-scale IQ in SSC probands (n = 2,581 subjects); the blue line denotes the linear relationship between all other *de novo* deletions and full-scale IQ in SSC probands (n = 2,581 subjects); shaded regions denote 95% confidence interval; red line p-value is associated with a Poisson regression predicting count of contributing *de novo* deletions from proband IQ and proband sex, and estimates the probability of no association between proband IQ and rate of contributing *de novo* deletions; blue line p-value is associated with a Poisson regression predicting count of non-contributing *de novo* deletions from proband IQ and proband sex and estimates the probability of no association between proband IQ and rate of non-contributing *de novo* deletions; control rate dots are calculated from n = 2,100 unaffected sibling controls.



Supplementary Figure 10

***De novo* deletions, but not duplications, in constrained genes were associated with ASD**

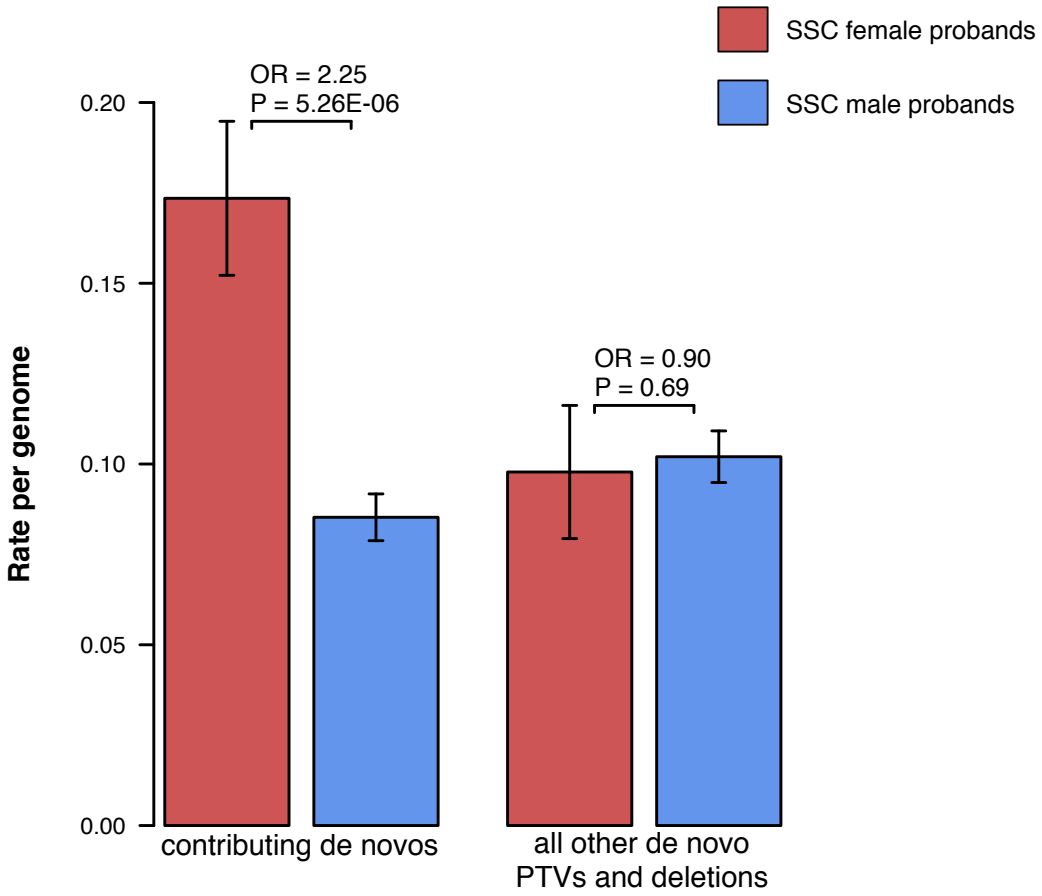
Rates are fraction of CNVs that include a constrained gene; p-values are from Fisher's exact test and estimate the probability with which case (n = 82 with duplication, n = 116 with deletion) and control (n = 27 with duplication, n = 45 with deletion) carriers are equally likely to have a deletion that includes a constrained gene.



Supplementary Figure 11

Association between CDNV rate and proband IQ in SSC

The red line denotes the linear relationship between rate of CDNVs (contributing *de novo* variants, **Online Methods: De novo *variant analyses***) and full-scale IQ in SSC probands (*n* = 2,340 subjects); the blue line denotes the linear relationship between all other *de novo* deletions and protein-truncating variants and full-scale IQ in SSC probands (*n* = 2,340 subjects); shaded regions denote 95% confidence interval; red line p-value is associated with a Poisson regression predicting count of CDNVs from proband IQ and proband sex, and estimates the probability of no association between proband IQ and rate of CDNVs; blue line p-value is associated with a Poisson regression predicting count of non-CDNV *de novo* deletions and PTVs from proband IQ and proband sex and estimates the probability of no association between proband IQ and rate of non-CDNV *de novo* deletions and PTVs; control rate dots are calculated from *n* = 1,736 unaffected sibling controls.



Supplementary Figure 12

Association between male:female carrier ratio and *de novo* variant category

P-values generated using Fisher's Exact test and estimate the probability that there is no difference between male proband (n = 2,029) and female proband (n = 317) variant rates; see **Online Methods: De novo *variant analyses*** for variant description.